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# Nitrogen- and Phosphorus-Containing Lewis Base Catalyzed [4+2] and [3+2] Annulation Reactions of Isatins with But-3-yn-2-one

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**Keywords:** Nitrogen heterocycles / Spiro compounds / Reaction mechanisms / Lewis bases

Nitrogen- and phosphorus-containing Lewis base catalyzed [4+2] and [3+2] annulations of isatins with but-3-yn-2-one proceeded smoothly to give the corresponding spiro[indoline-3,2′-pyran]-2,4′(3′*H*)-diones and spiro[furan-2,3′-indoline]-2′,4(5*H*)-diones in good-to-excellent yields under mild conditions. The substrate scope has been carefully examined. Moreover, the additive effect of water has also been investigated in detail along with plausible reaction mechanisms based on previous literature and our own investigations.

Oxindoles that incorporate a quaternary stereogenic center at C-3 are attractive targets in organic synthesis because of their significant biological activities as well as wide-ranging utility as intermediates in the synthesis of alkaloids, drug candidates, and clinical pharmaceuticals.[1,2] Therefore a number of useful synthetic methods have been developed in pursuit of this interesting structural motif, including intermolecular alkylations,[3] palladium-catalyzed couplings,[4] cycloadditions,[5] sigmatropic rearrangements,[6] carbanion nucleophilic additions to ketones or ketimines of isatin,[7] and annulations of allenoates.[8,9] Recently we reported an efficient method for the construction of this important structural motif through the annulation of isatin-derived electron-deficient alkenes with allenoates[10] and isatylidene malononitriles with Morita–Baylis–Hillman (MBH) carbonates in the presence of phosphanes.[11] Inspired by the results, we envisaged that by using but-3-yn-2-one as the reactant, novel spiro cycloadducts might be formed in nitrogen- or phosphorus-containing Lewis base catalyzed annulation reactions. In this paper we disclose a novel nitrogen-containing Lewis base mediated [4+2] annulation and an interesting phosphorus-containing Lewis base catalyzed [3+2] annulation of isatins with but-3-yn-2-one to produce the corresponding spiro[indoline-3,2′-pyran]-2,4′(3′*H*)-diones and spiro[furan-2,3′-indoline]-2′,4(5*H*)-diones, respectively, in good yields under mild conditions (Scheme 1).

## Results and Discussion

The investigation started with the reaction of *N*-Bn-protected isatin **1a** (1.0 equiv.) and but-3-yn-2-one (**2**; 1.5 equiv.) in the presence of 1,4-diazabicyclo[2,2,2]octane (DABCO; 20 mol-%) in THF at room temperature (20 °C). We found that the oxygen-containing six-membered cyclic product 1-benzylspiro[indoline-3,2′-pyran]-2,4′(3′*H*)-dione (**3a**) was obtained in 17% yield (Table 1, entry 1). The structure of product **3a** was assigned on the basis of spectroscopic analyses and unambiguously confirmed by X-ray diffraction of single crystals of **3a**. The ORTEP drawing of the structure is shown in Figure 1.[12] Increasing the amount of DABCO employed to 1.0 equiv. (100 mol-%) afforded product **3a** in 85% yield (Table 1, entry 2). However, further increasing the amount of DABCO employed to 1.2 or 1.5 equiv. did not improve the yield of product **3a** (Table 1, entries 3 and 4). When the reaction was carried out with **1**/**2**/DABCO = 1:1:1 or 1:2:1 in THF at room temperature, it was found that the corresponding annulation products **3a** were obtained in 73 and 85% yields, respectively (Table 1, entries 5 and 6). The use of other nitrogen-containing Lewis bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), triethylamine (TEA), 4-(dimethylamino)pyridine (DMAP), and diisopropylethylamine (DIPEA) did not lead to further improvements in the yield of **3a** (Table 1, entries 7–10), which indicates that DABCO is the best promoter for this reaction. An examination of solvent effects revealed that THF is the solvent of choice for this novel annulation reaction (Table 1, entries 11–14).

Having identified the optimal reaction conditions, we next set out to examine the substrate scope of this [4+2] annulation reaction catalyzed by DABCO by using various isatin derivatives **1** with different substituents on the benz-

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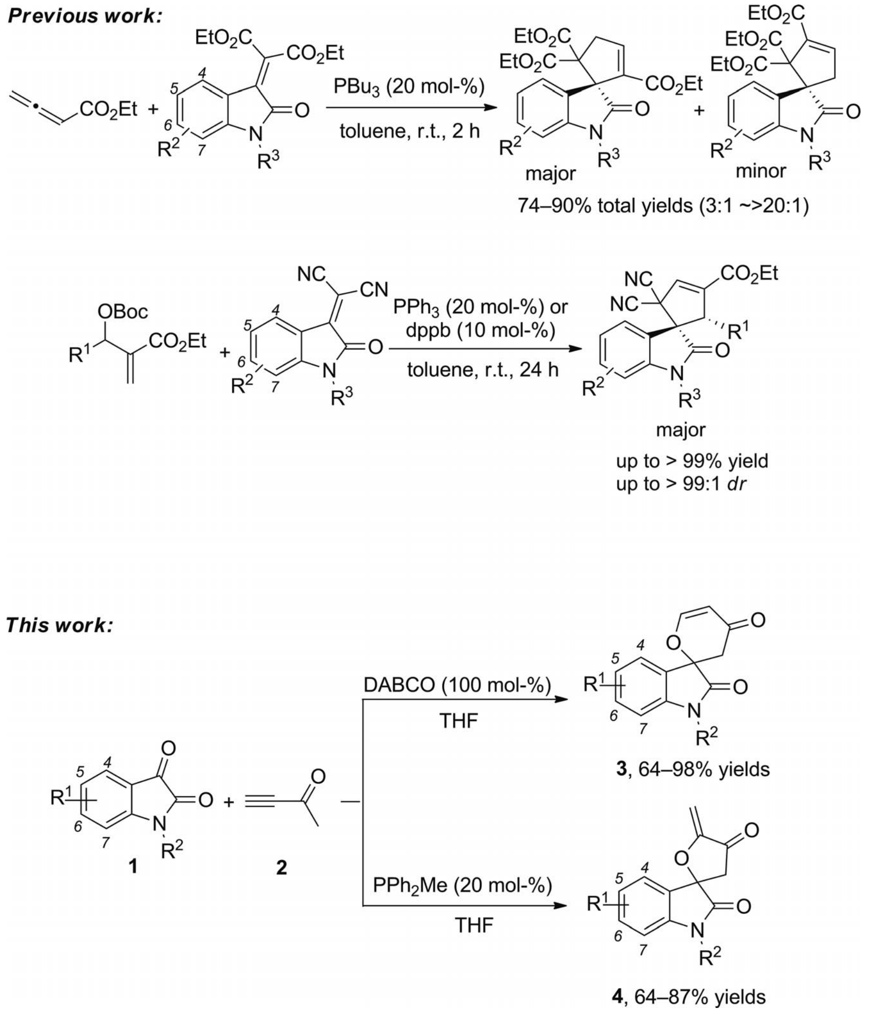


Scheme 1. Nitrogen- and phosphorus-containing Lewis base catalyzed [4+2] and [3+2] annulations.

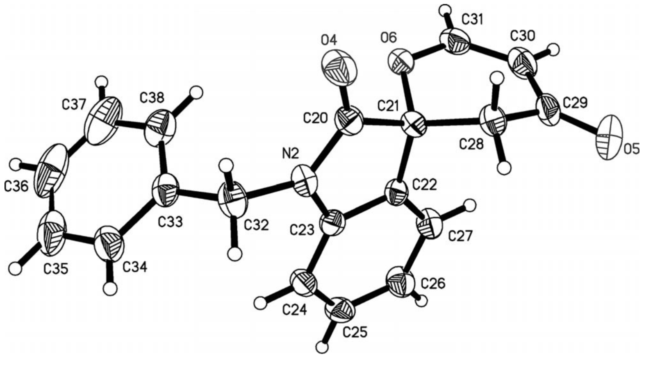
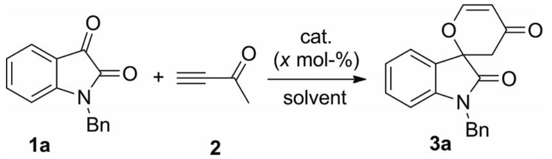


Figure 1. ORTEP drawing of the crystal structure of **3a**.

ene ring. The results are summarized in Table 2. The reactions proceeded smoothly to give the corresponding products **3b**–**3k** in moderate-to-good yields irrespective of whether electron-withdrawing or -donating groups were introduced at the 4-, 5-, 6-, or 7-position of the benzene ring of *N*-Bn-protected isatins **1**, which suggests that the electronic nature of the substituents does not have an impact on the reaction (Table 2, entries 1–10). Note also that the reactions of isatin derivatives **1l**–**1q** bearing different nitrogen protecting groups also proceeded efficiently to produce the corresponding spiro cycloadducts **3l**–**3q** in moderate-to-good yields (Table 2, entries 11–16). We also found that the products **3a**–**3q** are quite stable during their isolation by silica gel column chromatography.

We found that another spiro cycloadduct, 1′-benzyl-5-methylene-3*H*-spiro[furan-2,3′-indoline]-2′,4(5*H*)-dione (**4a**), was formed from a [3+2] annulation in 74% yield by using triphenylphosphane (20 mol-%) as the catalyst (Table 3, entry 1). Its structure was unambiguously determined by X-ray analysis of the single crystal of its analogue **4j** (see Table 4, entry 9). Its structure is shown in Figure 2.[13] Examination of various phosphane catalysts for this reaction indicated that $PPh_2Me$ is the best catalyst for this reaction (Table 3, entries 2–4). However, reducing or increasing the amount of but-3-yn-2-one (**2**) employed did not improve the yields of **4a** in the presence of $PPh_2Me$ (20 mol%; Table 3, entries 5 and 6). The use of 10 mol-% $PPh_2Me$ as catalyst produced **4a** in 61% yield (Table 3, entry 7). Solvent screening indicated that THF is still the solvent of choice for this interesting [3+2] annulation reaction (Table 3, entries 8–11).

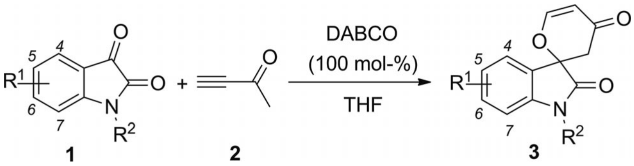
Table 1. Optimization of the conditions for the [4+2] annulation reaction.[a]



| Entry | 1a/2 | Cat. | x [mol-%] | Solvent | Yield [%][b] |
|---|---|---|---|---|---|
| 1 | 1:1.5 | DABCO | 20 | THF | 17 |
| 2 | 1:1.5 | DABCO | 100 | THF | 85 |
| 3 | 1:1.5 | DABCO | 120 | THF | 84 |
| 4 | 1:1.5 | DABCO | 150 | THF | 85 |
| 5 | 1:1 | DABCO | 100 | THF | 73 |
| 6 | 1:2 | DABCO | 100 | THF | 85 |
| 7 | 1:1.5 | DMAP | 100 | THF | 80 |
| 8 | 1:1.5 | DBU | 100 | THF | trace |
| 9 | 1:1.5 | $Et_3N$ | 100 | THF | 73 |
| 10 | 1:1.5 | DIPEA | 100 | THF | 56 |
| 11 | 1:1.5 | DABCO | 100 | toluene | 62 |
| 12 | 1:1.5 | DABCO | 100 | DCM | 75 |
| 13 | 1:1.5 | DABCO | 100 | $CH_3CN$ | 73 |
| 14 | 1:1.5 | DABCO | 100 | $Et_2O$ | 82 |

[a] Compound **1a** (0.2 mmol) and the catalyst were dissolved in solvent (2 mL) and then compound **2** was added to the reaction solution. The resulting reaction mixture was stirred for 0.5 h. [b] Isolated yields.

Table 2. Substrate scope of the [4+2] annulation reaction.[a]

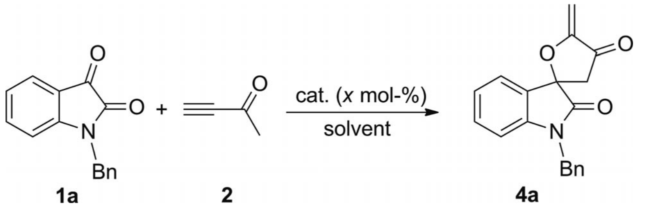


| Entry | R1 | R2 | Yield [%][b] |
|---|---|---|---|
| 1 | 5-F | Bn, **1b** | **3b**, 84 |
| 2 | 5-$CH_3$ | Bn, **1c** | **3c**, 82 |
| 3 | 5-Cl | Bn, **1d** | **3d**, 70 |
| 4 | 5-Br | Bn, **1e** | **3e**, 76 |
| 5 | 6-Br | Bn, **1f** | **3f**, 80 |
| 6 | 7-Br | Bn, **1g** | **3g**, 65 |
| 7 | 5,7-$(CH_3)_2$ | Bn, **1h** | **3h**, 73 |
| 8 | 4-Cl | Bn, **1i** | **3i**, 70 |
| 9 | 4-Br | Bn, **1j** | **3j**, 68 |
| 10 | 5-$CH_3O$ | Bn, **1k** | **3k**, 67 |
| 11 | 5-$CH_3$ | $CPh_3$, **1l** | **3l**, 66 |
| 12 | 5-Br | $CPh_3$, **1m** | **3m**, 68 |
| 13 | H | Me, **1n** | **3n**, 87 |
| 14 | H | allyl, **1o** | **3o**, 86 |
| 15 | H | $CPh_3$, **1p** | **3p**, 64 |
| 16 | H | (anthracen-10-yl)methyl, **1q** | **3q**, 65 |

[a] Compound **1** (0.2 mmol) and DABCO (0.2 mmol) were dissolved in THF (2 mL) and then compound **2** (0.3 mmol) was added to the reaction mixture. The resulting reaction mixture was stirred for 0.5 h. [b] Isolated yields.

The yield determined by $^1H$ NMR spectroscopic analysis of the crude using 1,3,5-trimethoxybenzene as internal standard was 97% (Table 3, entry 2), which indicates that product **4a** partially decomposed during the isolation process by silica gel column chromatography.

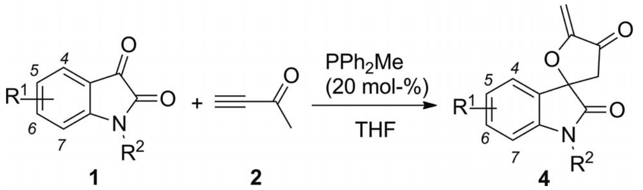
Table 3. Optimization of the conditions of the [3+2] annulation reaction.[a]



| Entry | 1a/2 | Cat. | x (mol-%) | Solvent | Yield [%][b] |
|---|---|---|---|---|---|
| 1 | 1:1.5 | $PPh_3$ | 20 | THF | 74 |
| 2 | 1:1.5 | $PPh_2Me$ | 20 | THF | 86 (97)[c] |
| 3 | 1:1.5 | $PPhMe_2$ | 20 | THF | 60 |
| 4 | 1:1.5 | $PBu_3$ | 20 | THF | 44 |
| 5 | 1:1 | $PPh_2Me$ | 20 | THF | 66 |
| 6 | 1:2 | $PPh_2Me$ | 20 | THF | 85 |
| 7 | 1:1.5 | $PPh_2Me$ | 10 | THF | 61 (59)[d] |
| 8 | 1:1.5 | $PPh_2Me$ | 20 | toluene | 63 |
| 9 | 1:1.5 | $PPh_2Me$ | 20 | DCM | 79 |
| 10 | 1:1.5 | $PPh_2Me$ | 20 | $CH_3CN$ | 73 |
| 11 | 1:1.5 | $PPh_2Me$ | 20 | $Et_2O$ | 83 |

[a] Compound **1a** (0.2 mmol) and the catalyst were dissolved in solvent (2.0 mL) and then compound **2** was added to the reaction mixture. The reaction mixture was stirred for 1 h. [b] Isolated yields. [c] The yield was determined by $^1H$ NMR spectroscopic analysis of the crude by using 1,3,5-trimethoxybenzene as internal standard. [d] The reaction mixture was stirred for 5 h.

Table 4. Substrate scope of the [3+2] annulation reaction.[a]



| Entry | R1 | R2 | Yield [%][b,c] |
|---|---|---|---|
| 1 | 5-F | Bn, **1b** | **4b**, 87 (82) |
| 2 | 5-$CH_3$ | Bn, **1c** | **4c**, 98 (83) |
| 3 | 5-Cl | Bn, **1d** | **4d**, 78 (74) |
| 4 | 5-Br | Bn, **1e** | **4e**, 88 (72) |
| 5 | 6-Br | Bn, **1f** | **4f**, 95 (76) |
| 6 | 7-Br | Bn, **1g** | **4g**, 65 (63) |
| 7 | 5,7-$(CH_3)_2$ | Bn, **1h** | **4h**, 92 (71) |
| 8 | 5-$CH_3O$ | Bn, **1i** | **4i**, 98 (73) |
| 9 | H | Me, **1j** | **4j**, 89 (88) |
| 10 | H | allyl, **1k** | **4k**, 82 (75) |
| 11 | H | $CPh_3$, **1l** | **4l**, 64 (61) |
| 12 | H | (anthracen-10-yl)methyl, **1m** | **4m**, 83 (79) |
| 13 | H | Boc, **1n** | **4n**, 90 (88) |
| 14 | H | mom, **1o** | **4o**, 83 (78) |

[a] Compound **1** (0.2 mmol) and $PPh_2Me$ (0.04 mmol) were dissolved in THF (2.0 mL) and then compound **2** (0.3 mmol) was added to the solution. The resulting reaction mixture was stirred for 1 h. [b] Isolated yields. [c] The yields given in parentheses were determined by $^1H$ NMR analysis of the crudes by using 1,3,5-trimethoxybenzene as internal standard.

Next we examined the substrate scope of this reaction by using a variety of isatin derivatives **1**. The results of these experiments are summarized in Table 4. In general we iso-

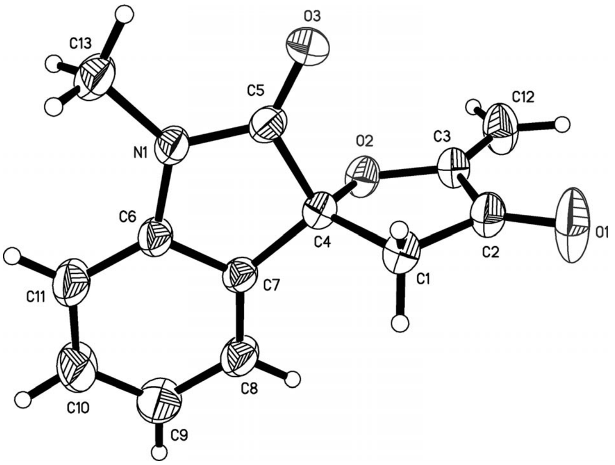
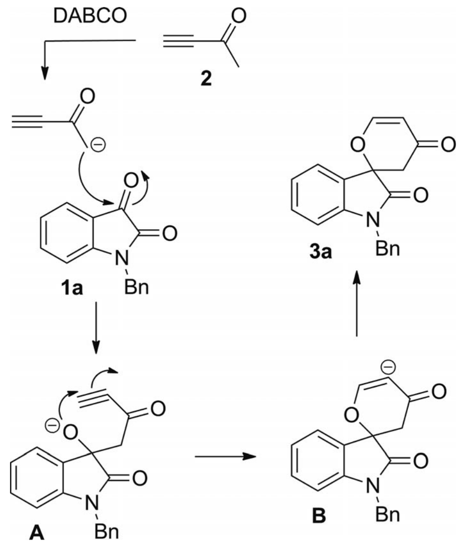


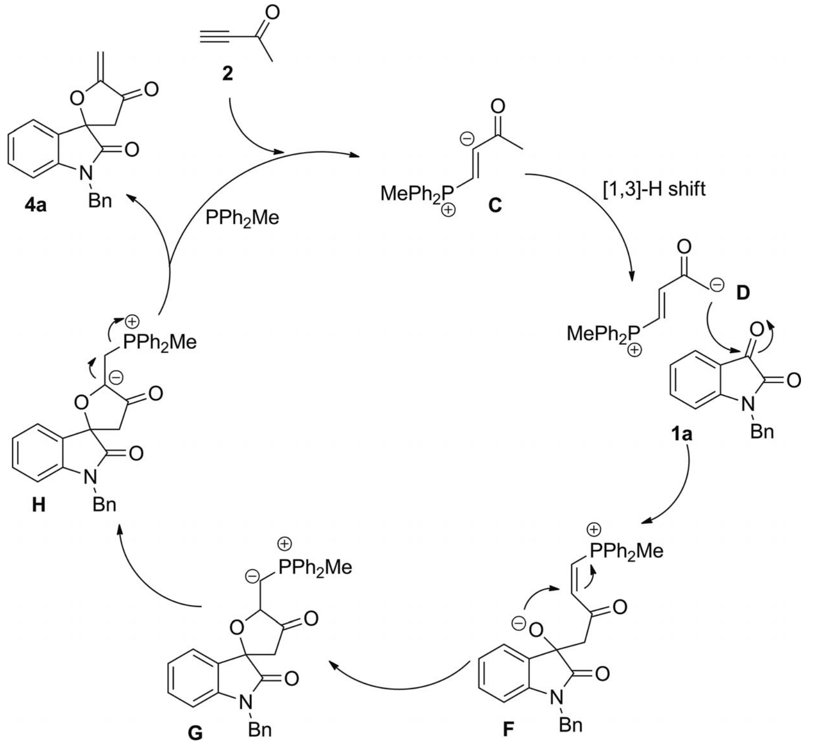
Figure 2. ORTEP drawing of the crystal structure of **4j**.

lated the oxygen-containing heterocyclic compounds **4** in moderate-to-good yields. All of the reactions proceeded smoothly under the standard conditions. The yields of the corresponding spiro five-membered heterocyclic products **4b**–**4i** were not influenced significantly by the electronic nature of the substituents on the benzene ring of **1** (Table 4, entries 1–8). Changing the nitrogen protecting group to methyl, allyl, $CPh_3$, (anthracen-10-yl)methyl, Boc, or mom (methoxymethyl) also afforded the corresponding products **4j**–**4o** in moderate-to-good yields, which suggests a wide substrate scope for this reaction (Table 4, entries 9–14). It should be emphasized here that these spiro cycloadducts are not very stable and that they decompose partially during the purification process (Table 4, entries 1–14). Their structures were determined by IR, NMR, and MS.

The mechanism for the formation of **3a** shown in Scheme 2 may be invoked to rationalize the reaction outcomes. Initially, as Lewis base, DABCO deprotonates but-3-yn-2-one (**2**) to generate an enolate intermediate.[14] Nucleophilic addition of this species to the carbonyl group of *N*-Bn-protected isatin **1a** gives intermediate **A**. Intramolecular Michael addition of the O$^-$ anion to the alkynyl group



Scheme 2. A plausible mechanism for the formation of **3a**.



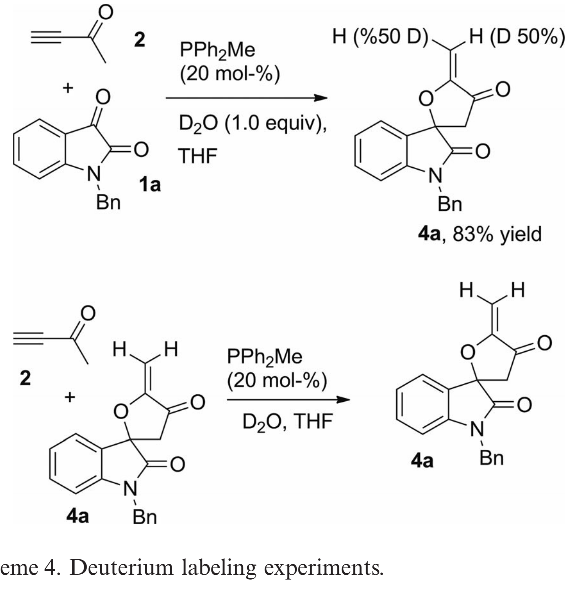
Scheme 3. A plausible mechanism of the formation of **4a**.

in intermediate **A** gives intermediate **B**, which subsequently undergoes protonation to produce the corresponding product **3a**. Because DABCO serves as a Brønsted base in this reaction, a stoichiometric amount of DABCO is required.

The mechanism for the formation of **4a** is proposed in Scheme 3. First, the reaction of $PPh_2Me$ with but-3-yn-2-one (**2**) generates the zwitterion intermediate **C**,[15] which undergoes a 1,3-hydrogen shift to give enolate intermediate **D**.[16] Nucleophilic addition of enolate **D** to the carbonyl group of *N*-Bn-protected isatin **1a** produces intermediate **F**. Intramolecular addition of the $O^-$ anion to the alkenyl group in intermediate **F** gives ylide-type intermediate **G**, which subsequently undergoes a 1,2-hydrogen shift to afford intermediate **H**. The elimination of phosphane gives the final product **4a**.[17]

Furthermore, the additive effects of water in the above reactions were also examined under the standard conditions and it was found that water can accelerate the phosphane-catalyzed annulation reaction, as reported by other groups (see the Supporting Information for details).[18] Note that the spiro cycloadducts are not very stable and they decompose slightly in the presence of water.

To gain more mechanistic insights we performed an isotopic labeling experiment by adding 1.0 equiv. of $D_2O$ to the reaction system; the reaction was carried out under the standard conditions (Scheme 4). It was found that the product [D]**4a** was obtained in 83% yield with 50% D content (see the Supporting Information for details). Control experiments suggested that product **4a** could not incorporate deuterium under the standard reaction conditions in the presence of $D_2O$ and thus the deuterium is incorporated during the reaction, which supports a stepwise mechanism.



Scheme 4. Deuterium labeling experiments.

## Conclusion

We have disclosed a facile synthetic procedure for the preparation of functionalized spiro-cyclohexaneoxindole and spiro-cyclopenteneoxindole derivatives in good-to-excellent yields by N- and P-containing Lewis base mediated/catalyzed annulation of *N*-protected isatins **1** with but-3-yn-2-one under mild conditions. The annulation protocol is suitable for a variety of *N*-protected isatin derivatives. Moreover, two plausible mechanisms have been proposed on the basis of previous literature reports. Efforts are underway to elucidate the mechanistic details of these two annulation reactions and to explore other annulation reactions with N- and P-containing Lewis bases.

## Experimental Section

**General Procedure for the Formation of 3a:** Under argon, *N*-protected isatin **1a** (0.2 mmol), but-3-yn-2-one (**2**; 0.3 mmol), DABCO (0.2 mmol), and THF (2.0 mL) were added to a Schlenk tube. The mixture was stirred at room temperature for 0.5 h and the reaction was monitored by TLC. Then the solvent was removed under reduced pressure and the residue was purified by flash column chromatography (silica gel, PE/EtOAc, 2:1) to afford compound **3a** as a white solid in 85% yield.

**General Procedure for the Formation of 4a:** Under argon, *N*-protected isatin **1a** (0.2 mmol), but-3-yn-2-one (**2**; 0.3 mmol), $PPh_2Me$ (0.04 mmol), and THF (2.0 mL) were added to a Schlenk tube. The mixture was stirred at room temperature until the reaction was complete. Then the solvent was removed under reduced pressure and the residue was purified by flash column chromatography (silica gel, PE/EtOAc, 5:1) to give compound **4a** as a white solid in 86% yield.

**Supporting Information** (see footnote on the first page of this article): $^1H$ and $^{13}C$ NMR spectra of the compounds shown in Tables 1–4.

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[13] Crystal data for **4j**: $C_{13}H_{11}NO_3$, $M_r$ = 229.23, colorless, 0.208 × 0.165 × 0.057 mm, orthorhombic, $a$ = 19.993(3), $b$ = 5.5764(9), $c$ = 10.1469(17) Å, $\alpha$ = 90, $\beta$ = 90, $\gamma$ = 90°, $V$ = 1131.3(3) Å$^3$, *Pca2*(1), $Z$ = 4, $D_{\text{calcd.}}$ = 1.346 g/cm$^3$, $F$(000) = 480, final $R$ indices [$I > 2\sigma(I)$]: $R1$ = 0.0574, $wR2$ = 0.1283. CCDC-823432 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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